HANDBOOK of TOXICOLOGY

Volume I

Acute Toxicities

Editor: SPECTOR

HANDBOOK of TOXICOLOGY

Volume I

Acute Toxicities of Solids, Liquids and Gases to Laboratory Animals

EDITED BY
WILLIAM S. SPECTOR

Prepared under the Direction of the Committee
on the Handbook of Biological Data
DIVISION OF BIOLOGY AND AGRICULTURE
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Foreword

These tables of data on Toxicology, prepared under Aero Medical Laboratory Contract No. AF 33(616)-2873 between the National Academy of Sciences and the Wright Air Development Center, comprise Volume I of the Handbook of Toxicology. Under the same contract, additional volumes are scheduled for publication in 1956. The contract is administered under direction of the Aero Medical Laboratory, Directorate of Research, Wright Air Development Center, Dr. George Kitzes acting as project director, Project No. 7159, "Health Hazards of Air Force Materials".

Data for tables in all volumes were contributed by experts in various areas of the fields represented. The tables were assembled by the Handbook Staff and reviewed by specialists in the subjects covered. The work was carried out under the direction of the Committee on the Handbook of Biological Data, operating under the Division of Biology and Agriculture of the National Academy of Sciences-National Research Council.

Acknowledgment is made, on behalf of the Committee, to the Wright Air Development Center, United States Air Force, for the foresight and scientific judgment inherent in the commission to prepare this Handbook; to Dr. W. F. von Oettingen of the National Institutes of Health, who devoted immeasurable time and energy to the compilation of the data appearing in this volume and who served as a constant guide and advisor in its preparation; to the National Research Council Committee on Toxicology, under the chairmanship of Dr. Harold C. Hodge, for encouragement and advice in planning the contents of the Handbook; to Dr. William O. Negherbon of the Handbook Staff whose tireless and patient effort in organizing and tabulating the data was a principal factor in the fruition of the project; to Mrs. Dorothy Dittmer and Miss Dorsey Parker for their careful proofreading; to Mrs. Nellie Brown and Mr. John Sobrofski for their excellent performance in drafting and typing the manuscript; to the biologists and toxicologists who gave generously of their time to serve as contributors and reviewers; and finally to all the Handbook staff members who were called upon to lend a hand in the multitude of tasks inherent in preparation of the book.

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Future Volumes

(Tentative Publication Date, 1956-57)

It is expected that subsequent volumes will include, but not necessarily be limited to, the following:

Volume II: Physical, Chemical, Biological, and Toxicological Properties of Antibiotic, Anthelmintic, Anti-amebic, and Antimalarial Compounds; A Survey of Chemical Carcinogenic Agents; Metabolites of Toxic Compounds.

Volume III: Physical, Chemical, Biological, and Toxicological Properties of: Insecticides, Fungicides, Rodenticides, and Herbicides; Residues of Pesticides on (or in) Foods; Minimum Lethal Concentrations of Pesticides to Domestic Animals, Farm Animals, and Wildlife.

Volume IV: Toxic and Venomous Animals; Toxic Plants; Alkaloids; Poisons and Poisoning (Compound, Symptoms, Antidote and Treatment); Histologic and Physiologic Effects of Poisons; Toxicities of Ingredients of Commonly Used Commercial Products; Toxicities of Natural Substances Occurring in Foods.

Volume V: Toxicities of Potential Water Pollutants; Maximum Allowable Concentrations of Toxic Substances in Air, Drinking Water, and Food; Agents and Symptoms of Chronic Toxicities; Skin Toxicities; Industrial Toxicology; Radiation Toxicology.

Introduction

This volume presents tabular data on the acute toxicity of various substances for several species of commonly used laboratory animals, as determined by oral or parenteral administration, or inhalation, of fatal doses.* The guiding principle in selection of material has been that it be of basic importance and from reliable literature sources. Some data of value have had to be omitted either because they were not on hand for publication or because time has not permitted the necessary preparatory steps for printing. The fact that certain data have been compiled and are already in print, or available in other form, has not been regarded as a reason for excluding them from the Handbook. Every page of this volume has been examined for accuracy by the contributors of the data and by a panel of review experts.

In tabulating this information the chief objective has been clarity of presentation. To maintain this clarity, only the most fundamental data appear in the body of the table. Footnotes have been used to supply additional facts in many instances so that simplification of the table structure could be achieved. Other material, pertinent to the values within the table but prohibited by the limitations of space, are to be found in the literature, and for this reason the reference for each line of data is presented on that line. Because of space limitations, only the principal author (initials omitted) is given for each reference. In several cases the values in the table have been calculated from the values in the references, e.g., from cc to mg/kg or from ions to salts. Chemical nomenclature, as it appears in the tables, has been kept exactly as contributed and is identical with that in the literature reference. Thus it may be that for some compounds proprietary names will be given and for others, official designations. However, a cross index at the back of the book contains a multitude of synonyms to facilitate location of any compound within the book.

It must be emphasized that the values presented in these tables are by no means absolute and should be interpreted only as a "yardstick" of toxicity for the compounds listed. Again, the literature reference, in most cases, will reveal the number of determinations, the number of animals in each determination, and conditions under which determinations were made. Some of the conditions which influence toxicity of any given compound are as follows:

a. Dose: Generally, the larger the dose the more rapid the action.
b. Rate of absorption: The faster this rate, the quicker the action of the drug. With oral administration the lethal dose may be considerably influenced by the condition of the gastrointestinal tract, especially by the amount of food and fecal material in the stomach and intestine.
c. Route of administration: For the most part, toxicity is greatest by the route that carries the toxic substance to the bloodstream most rapidly. In descending order of speed of action, routes for most drugs are: intravenous, inhalation, intraperitoneal, intramuscular, subcutaneous, oral, and cutaneous. Food in the alimentary canal may delay or decrease toxic action; digestive enzymes may destroy or alter the compounds with resultant changes in the toxicity thereof. Certain compounds are harmless if taken orally and lethal when introduced parenterally; in many cases the converse is true. The toxicity of the drug may also vary considerably with the form in which it is administered, i.e., solid, in suspension, or in solution. In the last instance the toxicity again may be influenced by the solvent and the concentration.
d. Site of injection: With subcutaneous injections, toxicity may be affected by the density of the subcutaneous tissue. With intravenous administration whether the injection is made into the femoral or jugular vein may be of importance, but in any case the rate of injection, or the amount of toxic material injected per minute, will considerably influence the value of the toxic dose.
e. Other influences: Disease, environmental temperature, habit and tolerance, idiosyncrasy, diet, season of the year (especially with hibernating animals) may all affect the toxicity of a drug. The toxicity of chemicals will also vary with the species of animals used, and sometimes with different strains of the same species. Within the same strain the toxicity may differ with age, weight, sex, and the general conditions of the animals.

* Volume II of the Handbook of Toxicology is scheduled to appear early in 1956.

With all of the above variables exerting their individual or collective influences, it is important that the toxicity be delineated with reference to the time of death or the period of time for which fatalities are counted.

Unfortunately, only in rare instances are all these factors considered and specified in the literature on toxicity determinations. This renders the duplication of such data by different investigators extremely difficult if not impossible. At the present time, attempts are being made to put toxicity data on a quantitative basis. The older literature often refers simply to "lethal doses" (LD) or "minimal lethal doses" (MLD), meaning doses which will be fatal or the smallest dose which will kill a limited number of animals. By using a larger number of animals of comparative weight and sex for each level tested, attempts are now being made to determine more precisely the dose which will kill 50 percent (LD_{50}). These values can be further certified by the application of various statistical methods, by stating the degree of deviation of the single values from the mean or the slope of the toxicity curve.

In each instance where a numerical value is given in this volume, that value may be considered as the mean (or adjusted mean) of a group of measured values taken from one literature source and usually determined by one investigator. Wherever given in the reference, each such value is followed by an estimate of the lower and upper limits of the 95% range, a direct representation of the ordinary range of variation. Further calculations from values in these tables should not be undertaken without information on comparability and number of measurements. As mentioned previously in this introduction, space does not permit the inclusion of such collateral information, but the bibliographic references will lead to the original data where it should be found.

The 95% range may be estimated in several ways, the method depending upon the information available. The types of estimate most widely used are listed below. Range data as commonly encountered, including estimates of the 95% range, represent a mixture of the variability existing between individuals and the variability existing within individuals.

a. By the method of greatest accuracy, the 95% range is obtained by fitting a recognized type of frequency curve to a group of measured values and excluding the extreme 2.5% of area under the curve at each end. Estimate is made by this procedure only when the group of values is relatively large.
b. By a less accurate method, the 95% range is estimated by a simple statistical calculation, assuming a normal distribution and using the standard deviation. This estimate is used when the group of values is too small for curve fitting, as is usually the case.
c. A third and still less accurate procedure for estimate of the 95% range is to take as range limits the highest value and lowest value of the reported sample group of measurements. It underestimates the 95% range for small samples (3 or 4 values) and overestimates for larger sample sizes, but may be used in preference to the preceding method when the sample shows convincing evidence that the variable is asymmetrical in distribution.
d. The upper and lower limits of the ordinary range of variation, as estimated by an investigator experienced in measuring the quantity in question and based solely on general experience, constitute still another estimate of the 95% range. The trustworthiness of limits so placed should not be underestimated.

Ranges appearing in this volume may fall into any one of the four estimates listed. In many instances range data were not available.

The data in each table are, in the judgment of the contributors and reviewers, as authentic as can be procured under the conditions as they exist. It is recognized, however, that all data, and particularly data in the field of acute toxicity, are subject to continuing revision as investigators standardize techniques and make more measurements. The user of the volume is warned against attributing significance to small differences from species to species. He is invited to submit any values or ranges he feels should be given consideration, and is particularly invited to add to the coverage of the tables.

Abbreviations

- DOSE† -

LD = Lethal Dose	The amount (dose) which kills an animal.
MLD = Minimum lethal dose	The smallest of several doses which kills one of a group of test animals.
LD_{50}	The amount (dose) which kills 50% of a group of test animals (usually 10 or more).
LD_{100}	The amount (dose) which kills 100% of a group of test animals (usually 10 or more).

† - When, in the symbols listed, D is replaced by C, substitute the word "concentration" for "dose" (e. g., LD = Lethal Dose; LC = Lethal Concentration).

- ROUTE OF ADMINISTRATION -

ct	= cutaneous	io	= intraocular
ic	= intracutaneous	ip	= intraperitoneal
ici	= intracisternal	iv	= intravenous
ice	= intracerebral	or	= oral
il	= intralumbar	rt	= rectal
im	= intramuscular	sc	= subcutaneous

- VEHICLE -

alc	= alcohol	det	= detergent
cot oil	= cotton oil	N saline	= normal saline
Dil	= diluted	Na salt	= sodium salt
Eth gly	= ethylene glycol	Par oil	= paraffin oil
G acacia	= gum acacia	pet oil	= petroleum oil
G arabic	= gum arabic	Prop gly	= propylene glycol
G traga	= gum tragacanth	sal	= saline
cello	= cellosolve	Ses oil	= sesame oil

Veg oil = vegetable oil

- MISCELLANEOUS -

*	= circa	mo	= month(s)
cont	= continuous	sec.	= secondary
da	= day(s)	Sev	= several
hr	= hours(s)	tert.	= tertiary
min	= minute(s)	wk	= week(s)

TOXICITY CLASSES

The toxicological data presented in this handbook are the result of extensive tests on laboratory animals. Frequently, toxicologists, industrial hygienists, industrial physicians, etc., are asked to translate these data into terminology that will readily describe the hazards associated with their use. Consequently, classes have been established to define the toxicity of a chemical material, in common terms, with reference to data obtained by specified animal tests. The following tabulation of toxicity classes is useful only for those data which are applicable.

COMBINED TABULATION OF TOXICITY CLASSES*

		Various Routes of Administration			
Toxicity Rating	Commonly Used Term	LD_{50} Single Oral** Dose Rats	Inhalation 4 hr Vapor Exposure Mortality 2/6-4/6 Rats	LD_{50} Skin Rabbits	Probable Lethal Dose for Man
1	Extremely toxic	1 mg or less/kg	<10 ppm	5 mg or less/kg	A taste, 1 grain
2	Highly toxic	1-50 mg	10-100	5-43 mg	1 teaspoon 4 cc
3	Moderately toxic	50-500 mg	100-1000	44-340 mg	1 ounce 30 gm
4	Slightly toxic	0.5-5 g	1000-10,000	35-2.81 g/kg	1 pint 250 gm
5	Practically non-toxic	5-15 g	10,000-100,000	2.82-22.59 g/kg	1 quart
6	Relatively harmless	15 g and more	>100,000	22.6 or more g/kg	>1 quart

* Hodge, H. C., and Sterner, J. H., American Industrial Hygiene Association Quarterly, 10:4, 93, Dec 1943.

** Standards for intravenous LD_{50} for rats and rabbits may be obtained approximately by dividing the oral toxicity standards for rats by 10.

TABLE I

LETHAL DOSES OF SOLID AND LIQUID COMPOUNDS:
LABORATORY ANIMALS

	Compound	Animal	Route	Dose	Dosage mg/kg
					Value
1	Abobioside	Cat	iv	LD_{50}	0.6992
2	Abomonoside	Cat	iv	LD_{50}	0.6790
3	Acetal	Rat	or	LD_{50}	4570
		Rabbit	ct	LD_{50}	8210
4	Acetaldehyde	Frog	sc	LD	800
		Mouse	sc	LD_{50}	560
		Rat	or	LD_{50}	1930
		Rat	sc	LD_{50}	640
		Rat	ip	LD_{100}	500
		Rabbit	sc	LD*	1200
		Rabbit	iv	LD*	300
5	Acetamide	Frog	sc	LD*	200
		Rat	or	LD_{50}	30,400
		Dog	iv	LD	>5000
6	p-Acetaminobenzaldehydethio-semicarbazone	Mouse	or	LD	950
7	1-Acetaminocarbazole	Rat	or	LD_{50}	>3000
8	2-Acetaminocarbazole	Rat	or	LD_{50}	>5000
9	3-Acetaminocarbazole	Rat	or	LD_{50}	>6000
10	2-Acetaminodibenzofuran	Rat	or	LD_{50}	>5000
11	3-Acetaminodibenzothiophene	Rat	or	LD_{50}	1195
12	3-Acetamino-9-methylcarbazole	Rat	or	LD_{50}	3115
13	p-Acetaminophenol	Rabbit	iv	MLD	3700
14	1-Acetamino-5,6,7,8-tetra-hydrocarbazole	Rat	or	LD_{50}	3865
15	3-Acetamino-5,6,7,8-tetra-hydrocarbazole	Rat	or	LD_{50}	>6000
16	Acetanilide	Mouse	sc	LD	1300[1]
		Rat	or	LD_{50}	800[2]
		Guinea pig	or	MLD	200
		Rabbit	or	LD	1500-1600
		Rabbit	or	LD	900-1200
		Cat	or,iv	LD	250
		Cat	iv	LD	8.5-13.5
		Dog	or	LD	700
		Dog	iv	LD	175-300
		Dog	iv	LD*	300-1200
17	Acetarsone[3]	Rat	or	LD	>4500
		Rat	im	LD	>140
		Guinea pig	or	MLD	100
		Rabbit	or	MLD	100
		Rabbit	or	LD_{50}	150

(continued on next page)

/1/ As a 55% solution in alcohol. /2/ As a 2% suspension in H_2O. /3/ Toxicity of different

Dosage mg/kg Range	Vehicle	Time of Death	Reference	
0.3732-1.1560	Alcohol		Chen, J. Pharm. Exp. Ther. 111:365, 1954.	1
0.4832-0.8365	Alcohol		Chen, J. Pharm. Exp. Ther. 111:365, 1954.	2
4240-4920			Smyth, J. Ind. Hyg. Tox. 31:60, 1949. Ibid	3
1620-2240		24 hr 14 hr 10 min 24 hr Instant	Supniewski, J. Pharm. Exp. Ther. 30:429, 1927. Skog, Acta pharm. tox. 6:299, 1950. Smyth, Arch. Ind. Hyg. Occ. Med. 4:119, 1951. Skog, Acta pharm. tox. 6:299, 1950. Stotz, J. Biol. Chem. 152:41, 1944. Supniewski, J. Pharm. Exp. Ther. 30:429, 1927. Ibid	4
28,300-32,600			Gibbs, Dubois' Arch. f. Physiol. Suppl. p259,1892. Smyth, unpublished data, Mellon Inst. Gibbs, Dubois' Arch. f. Physiol. Suppl. p259,1892.	5
		2-5 da	Savini, C. rend. Soc. biol. 144:1310, 1950.	6
			Eagle, J. Pharm. Exp. Ther. 99:450, 1950.	7
			Eagle, J. Pharm. Exp. Ther. 99:450, 1950.	8
			Eagle, J. Pharm. Exp. Ther. 99:450, 1950.	9
			Eagle, J. Pharm. Exp. Ther. 99:450, 1950.	10
			Eagle, J. Pharm. Exp. Ther. 99:450, 1950.	11
			Eagle, J. Pharm. Exp. Ther. 99:450, 1950.	12
			Hinsberg, Arch. exp. Path. Pharm. 33:216, 1894.	13
			Eagle, J. Pharm. Exp. Ther. 99:450, 1950.	14
			Eagle, J. Pharm. Exp. Ther. 99:450, 1950.	15
	Alcohol H_2O H_2O Alcohol		Hale, Hyg. Lab. Bull. 53, 1909. Smith, J. Pharm. Exp. Ther. 54:159, 1935. Lépine, Rev. de med. 306: 1887. Munch, J. Am. Pharm. Assoc. 30:91, 1941. Ibid Ibid Ibid Karczmar, Fed. Proc. 6:341, 1947. Munch, J. Am. Pharm. Assoc. 30:91, 1941. Gibbs, Dubois' Arch. f. Physiol. Suppl. p259,1892.	16
125-175		8-13da	Nelson, J. Pharm. Exp. Ther. 63:122, 1938. Ibid Leake, J. Am. Med. Assoc. 98:195, 1932. Ibid Anderson, Proc. Soc. Exp. Biol. Med. 27:267, 1930.	17

brands may vary.

	Compound	Animal	Route	Dose	Dosage mg/kg Value
17	Acetarsone[1] (concluded)	Rabbit	or	LD	1500
		Rabbit	iv	LD	120
		Cat	or	MLD	125-150
		Cat	or	LD_{50}	150
18	Acetic acid	Mouse	or	LD_{50}	4960
		Rat	or	LD_{50}	3310
		Rat	or	LD_{50}	3530
19	Acetic acid butyl ester	Rat	or	LD_{50}	14,130
		Rabbit	ct	LD_{50}	>20 cc
20	Acetic acid isopropyl ester	Rat	or	LD_{50}	6750
		Rabbit	ct	LD_{50}	>20 cc
21	Acetic anhydride	Rat	or	LD_{50}	1780
		Rabbit	ct	LD_{50}	4000
22	Acetone	Rat	or	LD_{50}	9750
		Rat	iv	LD	4750-6336
		Rabbit	or	LD	7920
		Rabbit	or	LD_{50}	5340
		Rabbit	iv	LD*	1584
23	Acetone cyanohydrin	Rat	ct	LD_{50}*	150
24	Acetonitrile[2]	Frog	sc	MLD	9100
		Mouse	sc	MLD	600
		Mouse	sc	MLD	700
		Rat	or	LD_{50}	3800
		Rat	sc	LD	500-3900
		Guinea pig	sc	LD	180-450
		Rabbit	ct	LD_{50}	5000
		Rabbit	sc	MLD	105
		Rabbit	sc	MLD	130
		Monkey	sc	LD	720-800
		Pigeon	im	LD	4000
25	Acetophenone	Rat	or	LD_{50}	900
		Rat	or	LD_{50}	3000
		Guinea pig	ct	LD_{50}	>20,000
		Rabbit	ct	LD_{50}	1760
26	Acetophenone-4-methoxy-3-methyl	Mouse	or	LD_{50}	3.6 cc
		Rat	or	LD_{50}	1.5 cc
27	o-Acetoxycinnamic acid	Rat	or	LD_{50}	3150
28	3-Acetoxy-6-dimethylamino-4, 4-diphenylheptane	Mouse	sc	LD_{50}	70
29	3-Acetoxy-6-dimethylamino-4, 4-diphenyl-5-methylhexane	Mouse	sc	LD_{50}	250
30	1-Acetoxy-3-dimethylamino-1, 1-diphenyl-2-methylpropane	Mouse	sc	LD_{50}	350
31	2-(Acetoxy-3,5-dimethylphenyl)-trimethylammonium iodide	Mouse	or	LD_{50}	>1500
		Mouse	iv	LD_{50}	3.3±0.15

/1/ Toxicity of different brands may vary. /2/ Toxicity varies with diet of animal.

Dosage mg/kg Range	Vehicle	Time of Death	Reference	
125-175		3-20 da	Raiziss, Arch. f. Derm. Syph. 25:799, 1932. Ibid Leake, J. Am. Med. Assoc. 98:195, 1932. Anderson, Proc. Soc. Exp. Biol. Med. 27:267, 1930.	17
4430-5550 3000-3660 3200-3880		36 hr 36 hr	Woodard, J. Ind. Hyg. Tox. 23:78, 1941. Ibid Smyth, Arch. Ind. Hyg. Occ. Med. 4:119, 1951.	18
11,840-16,650			Smyth, Arch. Ind. Hyg. Occ. Med. 10:61, 1954. Ibid	19
6160-7380			Smyth, Arch. Ind. Hyg. Occ. Med. 10:61, 1954. Ibid	20
1480-2130 2700-5920			Smyth, Arch. Ind. Hyg. Occ. Med. 4:119, 1951. Smyth, unpublished data, Mellon Inst.	21
9,070-10,480 4790-5950			Smyth, unpublished data, Mellon Inst. Walton, J. Pharm. Exp. Ther. 33:175, 1928. Ibid Smyth, unpublished data, Mellon Inst. Walton, J. Pharm. Exp. Ther. 33:175, 1928.	22
			Sunderman, Arch. Ind. Hyg. Occ. Med. 8:371, 1953.	23
			Rentz, Arch. int. pharmacod. 36:455, 1929. Wiesbader, Endocrinology, 20:100, 1936. Hunt, Arch. int. pharmacod. 12:447, 1904. Smyth, J. Ind. Hyg. Tox. 30:63, 1948. Hunt, Heffter's Hdb. 1.1:812. Ibid Smyth, J. Ind. Hyg. Tox. 30:63, 1948. Rentz, Arch. int. pharmacod. 36:455, 1929. Verbrugge, Arch. int. pharmacod. 5:161, 1899. Hunt, Heffter's Hdb. 1.1:812. Meurice, Arch. int. pharmacod. 7:11, 1900.	24
800-1000 1670-1850			Smyth, unpublished data, Mellon Inst. Smyth, J. Ind. Hyg. Tox. 26:269, 1944. Ibid Smyth, unpublished data, Mellon Inst.	25
			Draize, J. Pharm. Exp. Ther. 93:76, 1948. Ibid	26
			Eagle, J. Pharm. Exp. Ther. 99:450, 1950.	27
			Eddy, J. Pharm. Exp. Ther. 98:121, 1950.	28
			Eddy, J. Pharm. Exp. Ther. 98:121, 1950.	29
			Eddy, J. Pharm. Exp. Ther. 98:121, 1950.	30
			Randall, J. Pharm. Exp. Ther. 99:16, 1950. Ibid	31